ORIGINAL ARTICLE

Effect of PGG-glucan on the Rate of Serious Postoperative Infection or Death Observed After High-Risk Gastrointestinal Operations

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Background: Postoperative infections remain common after high-risk gastrointestinal procedures. PGG-glucan (Betafectin; Alpha Beta Technology Inc, Worcester, Mass), derived from yeast cell walls, promotes phagocytosis and intracellular killing of bacterial pathogens by leukocytes, prevents infection in an animal model of wound infection, and acts synergistically with antibiotics to reduce mortality in rat peritonitis.

Hypothesis: We hypothesized that infectious complications in these patients might be reduced by the administration of a nonspecific immune-enhancing agent.

Design: Multicenter, prospective, randomized, double-blind, placebo-controlled trial of 1249 patients prospectively stratified into colorectal or noncolorectal strata.

Setting: Thirty-nine medical centers throughout the United States.

Patients: Aged 18 years or older, scheduled for gastrointestinal procedure lasting 2 to 8 hours, with 2 or more defined risk factors.

Interventions: PGG-glucan, 0.5 mg/kg or 1.0 mg/kg, or placebo once preoperatively and 3 times postoperatively. All patients received standardized antibiotic prophylaxis.

Main Outcome Measures: Serious infection or death within 30 days.

Results: All randomized patients revealed no difference in serious infections and deaths in the treated groups compared with placebo groups (15% vs 14%, $P>.90$). In the prospectively defined noncolorectal stratum (n = 391), PGG-glucan administration was associated with a statistically significant relative reduction (39%) in serious infections and death (placebo, 46 [36%] of 129 vs either PGG-glucan group, 29 [21%] of 132 and 28 [22%] of 130, $P<.02$). PGG-glucan reduced postoperative infection or death in malnourished patients having noncolorectal procedures (31 [44%] of 70, placebo group; 16 [24%] of 68, 0.5-mg/kg PGG-glucan group; 12 [17%] of 72, 1.0-mg/kg PGG-glucan group; $P<.001$). Study drug was stopped owing to adverse effects more frequently for patients receiving PGG-glucan than placebo (2%, 4%, and 7% for the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively, $P<.003$).

Conclusion: Perioperative administration of PGG-glucan reduced serious postoperative infections or death by 39% after high-risk noncolorectal operations.

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DESPITE MODERN surgical techniques and perioperative prophylactic antibiotics, postoperative infection rates are an ongoing cause for concern in high-risk patients. This risk is increased in patients having gastrointestinal procedures with potential endogenous bacterial contamination, especially with additional risk factors including lengthy procedures, preexisting illnesses, advanced age, diabetes mellitus, morbid obesity, malnutrition, and immunosuppression. We hypothesized that infectious complications in these patients might be reduced by the administration of a nonspecific immune-enhancing agent.

PGG-glucan is a yeast cell wall–derived glucose polymer, poly([1-6]β-D-glucopyranosyl-[1-3]β-D-glucopyranose),[1] with a high affinity for β-glucan receptors on human monocytes and neutrophils that binds competitively in a dose-dependent fashion.[2,3] PGG-glucan increases in vitro deuterium production[4] and the microbicidal activity of human neutrophils and monocytes against *Staphylococcus aureus* and *Escherichia coli*,[5] but it does not directly stimulate synthesis of interleukin 1[2,6-8] or tumor necrosis factor.[6-8] In vivo studies in mice and rats receiving PGG-glucan demonstrate improved survival compared with controls after challenge with *S aureus*, *E coli*, or cecal contents in peritonitis models.[7,9]

The affiliations of the authors appear in the acknowledgment section at the end of the article. A complete list of the members of the Betafectin Gastrointestional Study Group is given on page 982 of this article.

PATIENTS, MATERIALS, AND METHODS

This was a multicenter, double-blind, placebo-controlled, randomized trial conducted at 39 medical centers in the United States. All patients gave informed consent approved by the local institutional review board. Inclusion and exclusion criteria are given in **Table 1** and **Table 2**. Randomization was accomplished at a central facility and was prospectively stratified by center and by stratum (colorectal stratum, planned procedure involving incision in the colon or rectum; or noncolorectal stratum, no incision planned). Patients received 4 doses of study drug (placebo, 0.5 mg/kg of PGG-glucan or 1.0 mg/kg of PGG-glucan) suspended in sodium chloride injection, to a total volume of 250 mL. The maximum dose of PGG-glucan was 90 mg for patients weighing 90 kg or more. The doses were chosen from the prior clinical trials. The first dose was administered within 12 hours prior to the surgical incision; the second immediately after the operation, but at least 4 hours after the first dose; the third 48 (±4) hours after the start of the operation; and the fourth 96 (±4) hours after the start of the operation. All persons were completely blinded regarding drug assignment. Study blinding was maintained until all determinations regarding study outcome and protocol compliance had been determined, an independent adjudication panel of 4 infectious disease physicians and a surgeon with experience in infectious disease trials (Mitchell Fink, MD; Deborah Cotton, MD; Allen Kaiser, MD; David Syndman, MD; and Dori Zaleznik, MD) had completed their evaluation of the data, and the data set had been locked.

All patients received antibiotic prophylaxis according to protocol. Patients having colorectal operations had a mechanical bowel preparation combined with neomycin plus either erythromycin or metronidazole during the 18 hours prior to the procedure. These patients received 1 to 2 g of cefotetan intravenously, and those having a noncolorectal operation received 1 to 2 g of cefazolin intravenously during the 2 hours prior to incision. Cefotetan and cefazolin were given for 24 hours or less. Patients allergic to these antibiotics were not enrolled in the study.

Patients were followed up in the hospital and 30 to 45 days postoperatively. Serious infections were prospectively defined as a surgical site infection (SSI) either of the organ space or incision,[16] pneumonia, bloodstream infection, sepsis syndrome with any infection not otherwise defined, and any infection that led to a rehospitalization. The following definitions were used.

An *organ space SSI* was present if there was evidence of infection or abscess during reoperation or by radiological examination within the abdomen or chest directly related to the site of operation accompanied by a temperature greater than 38.0°C, a white blood cell count greater than 11.0×10^9/L and a pathogen was identified by Gram stain or culture or purulent material was obtained at operation or by needle aspiration, or by drain placed percutaneously into the organ space subsequent to the completion of the index operative procedure.

An *incisional SSI* was present if the patient had a temperature greater than 38.0°C, a white blood cell count greater than 11.0×10^9/L, localized signs of inflammation at the incision, or evidence of infection was found on direct examination of the incision, and the incision spontaneously dehisced or was deliberately opened by the surgeon or was percutaneously drained.

Pneumonia had to be evaluated by sputum examination with Gram stain and culture and by chest x-ray film and had to meet at least 1 each of the 5 following criteria: (1) temperature greater than 38.0°C, a white blood cell count greater than 11.0×10^9/L, respiratory rate greater than 20/min, minute ventilation greater than 10 L/min or $PaCO_2$ less than 32 mm Hg, chills, or altered mental state in the absence of other explanation; (2) chest pain, cough, rales, or dullness to percussion in nonventilated patients; (3) chest radiographic examination with new or progressive infiltrate, consolidation, cavitation, or pleural effusion; (4) purulent sputum with more than 25 polymorphonuclear leukocytes and less than 10 epithelial cells per low-power field; (5) culture-positive sputum with pure growth of a presumed pathogen, sputum Gram stain with predominant morphology consistent with a presumed pathogen, or positive blood culture for a respiratory pathogen.

A bloodstream infection was present if there was a temperature greater than 38.0°C, a white blood cell count greater than 11.0×10^9/L, chills, or altered mental state in the absence of other explanations and the patient had either a recognized pathogen from a single blood culture or 2 blood cultures drawn on separate occasions growing the same "skin contaminant" judged by the physician to represent an infection.

PGG-glucan prevented infections in a guinea pig model of wound infection.[10] In a rat model of polymicrobial peritonitis, PGG-glucan reduced mortality from 75% to 8%, and this effect could be transferred with spleen cells, spleen cell lysates, peripheral blood leukocytes, or serum from treated animals.[11] PGG-glucan was synergistic with antibiotic treatment in the same peritonitis model.[7,12] PGG-glucan does not have a reproducible pyrogenic effect in humans at therapeutic doses.[4,13]

Two phase 2 human trials have been conducted with PGG-glucan. In a single-center study comparing placebo with 0.5 mg/kg of PGG-glucan in 34 patients undergoing high-risk major abdominal or thoracic operations, the number of infections per infected patient was less in the group receiving PGG-glucan.[14] A subsequent multicenter trial involving 67 patients undergoing the same spectrum of procedures compared placebo, 0.1 mg/kg, 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg of PGG-glucan[15] and demonstrated a trend toward fewer infections with increasing doses of PGG-glucan. The difference in number of infected patients was not statistically significant in either trial.

RESULTS

Twelve hundred forty-nine patients were randomized at 39 centers in the United States between March 16, 1995, and February 28, 1997. Seventy-two patients were withdrawn before the administration of study drug, leaving 1177 patients (396 in the placebo group, 396 in the 0.5 mg/kg PGG-glucan group, and 385 in the 1.0 mg/kg PGG-glucan group) who received at least 1 partial dose of the

Sepsis syndrome was present if the patient had a temperature greater than 38.0°C, a pulse rate greater than 90 beats per minute, and a respiratory rate greater than 20 beats per minute or minute ventilation greater than 10 L/min or $PaCO_2$ less than 32 mm Hg, and 1 of the following: (1) systolic blood pressure < 90 mm Hg or a fall in systolic blood pressure greater than 40 mm Hg for more than 1 hour; (2) pharmacological vasopressors required to maintain a mean arterial pressure of greater than 55 mm Hg; (3) PaO_2 of less than 70 mm Hg on room air or PaO_2/FIO_2 ratio of less than 333 in the absence of pneumonia; (4) metabolic acidosis with pH less than 7.3 with no other cause for acidosis; (5) oliguria with urine output less than 0.5 mg/kg per hour for at least 1 hour; (6) abnormal coagulation suggesting disseminated coagulation such as prothrombin time greater than 150% of control, partial thromboplastin time greater than twice normal or fibrin degradation products greater than 10 mg/L; (7) significant alteration of mental status consisting of a decrease of at least 2 points on the Glasgow Coma Scale.

Any infection not defined above that resulted in a readmission of a patient to the hospital was defined as an infection requiring rehospitalization and was counted as a serious infection for the primary end point.

The principal investigator documented the elements of the definition for each serious infection, and these were verified by study monitors. At the conclusion of the study, prior to unblinding, the adjudication panel reviewed all infections and suspected infections to determine serious infections as defined by the protocol and to assign a predominant pathogen to each infection. The panel used the protocol definitions of serious infections as guidelines, but invoked clinical judgment in cases where they judged that infection was apparent but not all defined criteria were documented. Most decisions were made by consensus. When necessary, majority vote ruled. In the case of a tie, the principal investigator's assessment was used.

SAMPLE SIZE

Assumptions used to project sample size were that the serious infection rate in the placebo arm of the trial would be approximately 30%. Assuming a reduction in the treatment arm to an infection rate of 20%, approximately 1170 patients, equally allocated among 3 treatment groups, would be needed to detect a difference with 90% power and an α level of significance of .05.[17]

STATISTICAL ANALYSIS

The primary analysis was performed on an intent-to-treat group consisting of all patients who were randomized and received at least 1 partial dose of study drug (PGG-glucan or placebo group), irrespective of study eligibility criteria and operative status (all patients treated). Study results were also analyzed for an efficacy-evaluable group that consisted of all patients in the primary analysis group who met all inclusion/exclusion criteria, underwent a surgical procedure within 48 hours of the first infusion of study drug, received at least 2 complete doses of the study drug, and had documented day 30 infection status. Study results were also analyzed for each stratum (colorectal and noncolorectal) and descriptive statistics were provided.

Treatment comparisons were based on 2-sided tests. Categorical variables for preoperative data were assessed for treatment differences using a Cochran-Mantel-Haenszel χ^2 test adjusting for investigators and stratum. Continuous variables were assessed for treatment differences by analysis of variance with effects for treatment, investigator, stratum, and their interactions. The overall treatment effect for the primary end point (proportion of patients with serious infection or death) was determined by logistic regression with effects for treatment alone without adjustment for covariates.

The primary end point was analyzed for both the adjudicated infection status and investigator-reported infection status. Patients who died before day 30 were classified as a treatment failure. Patients with follow-up for fewer than 30 days were analyzed in 2 ways: (1) the primary analysis used a last infection status carried forward definition; (2) the alternate analysis counted all patients with fewer than 30 days of known infection status as a treatment failure.

A multivariate logistic regression analysis was used to investigate the potential effects of covariates of host and operative risk factors (noncolorectal stratum, wound class, age, duration of surgery, duration of preoperative stay, American Society of Anesthesiologists score, obesity status, diabetic status, malnutrition, and preexisting illness), and treatment effects. Serious infections were analyzed for both adjudicated and investigator-determined infection status using both methods of determining follow-up status described for the primary end point. Treatment effects were tested using a Cochran-Mantel-Haenszel statistic for differences in mean scores adjusting for investigator and stratum.

study drug and therefore constituted the intent-to-treat group. The results and conclusions are essentially the same for the efficacy-evaluable patients (n = 1100).

Of the 1177 patients, 786 were assigned to the colorectal stratum and 391 to the noncolorectal stratum. The distribution of operative procedures within these strata is displayed in **Table 3**. The preoperative randomization of 64 of the colorectal patients and 6 of the noncolorectal patients differed from the procedure actually performed based on intraoperative findings. These procedures are analyzed within the strata to which they were initially assigned. The demographics, potential risk factors, and selected operative parameters between these strata are displayed in **Table 4**. Within each strata there were no important differences between the 3 study treatment groups in any of these parameters except for a slight increase in the number of patients with a prolonged preoperative stay in the 0.5-mg/kg PGG-glucan group. However, significant differences were noted between the colorectal and noncolorectal strata for most prospectively defined variables (Table 4). The differences in the colorectal vs noncolorectal strata were further highlighted by a comparison of infection rates and/or death for the placebo groups (14% vs 36% for the colorectal and noncolorectal groups, respectively). A higher infection rate was observed in the noncolorectal stratum for each category of infection. More noncolorectal patients received postoperative nonprophylactic antibiotics (137 [47%] of 288 of noninfected patients [mean, 10 days]) than in the colorectal group (237 [35%] of 672 of noninfected patients [mean, 9 days]; $P<.001$), suggesting a more complicated and high-risk patient population.

Table 1. Inclusion Criteria

- Age ≥18 y
- Scheduled for an elective gastrointestinal operation with incision into stomach, intestine, colon, pancreas, or biliary tract
- Expected duration of operation 2 to 8 h with primary closure of the skin incision
- At least 2 of the following risk factors:
  - Gastric operation in the presence of achlorhydria, malignant ulcer, or obstruction
  - Biliary procedure with known common duct stones, recent elevated bilirubin (>25.6 μmol/L [1.5 mg/dL]), or planned common duct exploration
  - Colon or rectal operation
  - Pancreatic operation
  - Malnutrition, defined as 10% weight loss within 6 mo or serum albumin level <35 g/L
  - Age >60 y
  - Morbid obesity, body mass index ≥35 kg/m²
  - Diabetes mellitus, type 1 or type 2
  - Preoperative hospitalization ≥3 d
  - Preexisting illness, defined as ≥3 medical diagnoses requiring drug therapy

Table 2. Exclusion Criteria

- Operation for uncomplicated appendicitis or cholecystitis
- Operation for morbid obesity, pancreatitis, or active inflammatory bowel disease
- Laparoscopic procedure without at least a 2-h open incision planned
- Planned reoperation (other than tracheostomy or vascular access) or rehospitalization within 30 d
- Life expectancy <60 d
- Karnofsky status ≤20
- Systemic immunosuppressive therapy within 7 d before or after the operation
- Diagnosis of acquired immunodeficiency syndrome
- Absolute neutrophil count ≤1×10⁹/L
- Renal failure requiring dialysis
- Evidence of infection with antibiotic treatment within 5 d of the operation
- Known sensitivity to yeast
- Allergy to cephalosporins or severe allergy to penicillin
- Patient had previously received PGG-glucan or had been enrolled in any clinical trial within 30 d
- Antibiotic prophylaxis planned to extend for >24 h
- Pregnant or lactating

There was not a significant difference in end point events (serious infection and/or death) in the intent-to-treat group (84 [21%], 69 [17%], and 64 [17%] in the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively; $P>.02$). Based on the study design that prospectively identified enrolled patients as belonging to either the colorectal or noncolorectal strata and supported by the marked differences in demographics, risk factors, operative conduct, and outcomes between these 2 groups, the treatment effects of PGG-glucan vs placebo were analyzed separately for the colorectal and noncolorectal strata. Examination of the colorectal stratum failed to demonstrate any significant treatment effect. End point events were 38 (14%), 40 (15%), and 36 (14%) in the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively ($P=.93$).

Table 3. Operations Performed

Stratum	Group* Placebo	0.5-mg/kg PGG-Glucan	1.0-mg/kg PGG-Glucan
Colorectal (n = 786)			
Colectomy, intra-abdominal anastomosis	130	123	127
Colectomy, low rectal anastomosis	43	43	29
Colectomy, no anastomosis	10	29	13
Abdominal-perineal resection	24	13	19
Colostomy closure	23	15	14
Major colorectal procedure with multiple organ involvement	11	13	14
Create/revise colostomy	5	2	8
Other colorectal procedure	4	4	6
Noncolorectal procedure	17	22	25
Noncolorectal (n = 391)			
Esophagectomy	14	12	12
Gastrectomy	16	19	18
Pancreaticoduodenectomy	15	22	27
Other pancreatic procedure	13	19	15
Biliary procedure, no hepatic resection	17	17	21
Hepatic resection	7	4	3
Biliary and gastric bypass	8	5	7
Small intestinal procedure	16	10	4
Exploratory laparotomy with or without biopsy	4	9	5
Other gastric procedure	15	12	13
Major noncolorectal procedure with multiple organ involvement	2	2	5
Colorectal procedure	4	2	0

**For the colorectal stratum, n = 267 in the placebo group, n = 264 in the 0.5-mg/kg PGG-glucan group, and n = 255 in the 1.0-mg/kg PGG-glucan group. For the noncolorectal stratum, n = 129 in the placebo group, n = 132 in the 0.5-mg/kg PGG-glucan group, and n = 130 in the 1.0- mg/kg PGG-glucan group.*

In the noncolorectal stratum, important treatment effects were observed (**Table 5**). The 36% incidence of infection and death in the placebo group vs the 22% incidence in each of the treatment groups represents a 39% relative reduction in major adverse end points ($P<.02$). The greatest effect occurred in the reduction of organ space infection and pneumonia. The trends, conclusions, and significance do not change if the analyses are repeated using any of the different methods for determining failure (**Table 6**).

An analysis of covariates of infection revealed differences between the noncolorectal stratum and the entire group. Patients in the noncolorectal stratum had a 62% increased risk of serious infection compared with the colorectal stratum. The entire treated patient population demonstrated a significantly increased risk of infection associated with malnutrition, diabetes mellitus, contaminated or dirty wound classification, and duration of surgical procedure longer than 3 hours.

In the noncolorectal stratum, there was a significant increase in infection risk associated with malnutrition, obesity, and duration of operation longer than 3 hours. There was also a strong interaction between study drug and malnutrition. Because of this, a further analysis of malnourished patients in the noncolorectal stra-

Table 4. Demographics, Risk Factors, and Operative Conduct of Study Population, by Anatomical Stratum*

	Colorectal (n = 786)	Noncolorectal (n = 391)	P
Potential risk factors†			
Age ≥60 y	650 (83)	261 (67)	<.001
Obesity†	45 (6)	24 (6)	NS
Contaminated or dirty wound classification	85 (11)	36 (9)	NS
American Society of Anesthesiologists ≥3	435 (55)	243 (62)	<.05
Malnutrition‡	176 (22)	210 (54)	<.001
Diabetes mellitus‡	156 (20)	97 (25)	.05
≥3 Diagnoses‡	226 (29)	100 (26)	NS
Preoperative stay ≥3 d	149 (19)	125 (32)	<.001
Selected operative parameters			
Mean duration of operation, h	2.9	3.9	<.001
Mean duration endotracheal intubation, h	6.6	14.6	<.005
Central venous catheter	228 (29)	235 (60)	<.001
Arterial catheter	285 (36)	260 (66)	<.001
Drains	225 (29)	251 (64)	<.001
Intraoperative transfusion	128 (16)	90 (23)	<.05

*Data are presented as number (percentage) of patients unless otherwise indicated. NS indicates not significant.
†Prospectively defined covariates.
‡See text for definitions.

Table 5. Proportion of Patients With Serious Infection and Deaths Within 30 Days, Noncolorectal Stratum

	Group, No. (%)		
	Placebo (n = 129)	0.5-mg/kg PGG-Glucan (n = 132)	1.0-mg/kg PGG-Glucan (n = 130)
Patients with serious infections*	42 (33)	29 (22)	22 (17)
Organ space infection	13 (10)	6 (5)	7 (5)
Incisional site infection	10 (8)	10 (8)	6 (5)
Pneumonia	12 (9)	5 (4)	5 (4)
Bloodstream with sepsis	1 (1)	3 (3)	2 (2)
Bloodstream without sepsis	5 (4)	6 (5)	4 (3)
Sepsis syndrome without diagnosed infection	2 (2)	2 (2)	0 (0)
Other infection leading to rehospitalization	3 (2)	4 (3)	0 (0)
Deaths among infected patients	7 (5)	6 (5)	4 (3)
Death without serious infection by day 30	4 (3)	0 (0)	6 (5)
Total No. of end point events†	46 (36)	29 (22)	28 (22)

*Four patients had multiple infections in the placebo group, 4 in the 0.5-mg/kg PGG-glucan group, and 2 in the 1.0-mg/kg PGG-glucan group.
†P<.02.

Table 6. Percentage of End Point Events by Method of Counting, Noncolorectal Stratum*

		Group, %			
Method	No.	Placebo	0.5-mg/kg PGG-Glucan	1.0-mg/kg PGG-Glucan	P
All patients, adjudicated†	406	34	21	21	<.02
ITT, investigator's opinion‡, last status§	391	37	21	26	<.02
ITT, adjudicated, last status§	391	36	22	22	<.02
ITT, investigator's opinion, LTFU‖	391	40	24	28	<.03
ITT, adjudicated, LTFU	391	38	25	24	<.03

*ITT indicates intention-to-treat group; LTFU, lost to follow-up.
†Opinion of adjudication panel regarding endpoint event.
‡Investigator's opinion as recorded on case report form regarding endpoint event.
§For patients lost to follow-up before 30 days, status at last follow-up recorded as final status.
‖Lost to follow-up counted as failure.

tum was performed. The effect of the study drug in the malnourished patients having a noncolorectal procedure was striking, with serious infection or death occurring in 31 (44%) of 70, 16 (24%) of 68, and 12 (17%) of 72 patients in the placebo, 0.5-mg/kg PGG-glucan, and 1.0-mg/kg PGG-glucan groups, respectively ($P<.001$). Among the most common serious infection types, most of the pathogens identified were aerobic pathogens, including mixed facultative and aerobic pathogens, *S aureus*, and coagulase-negative staphylococcal species. The incidence of pathogens identified in the PGG-glucan groups were not different from those in the placebo group.

Evidence of adverse effects of PGG-glucan were sought among the combined strata. Forty-four patients (3.7%) died within 30 days, 21 of whom were infected and and 23 of whom were not. There were 16 in the placebo group, 13 in the 0.5-mg/kg PGG-glucan group, and 15 in the 1.0-mg/kg PGG-glucan group, with no significant differences among these groups for patients who died with or without infection. The causes of death in patients without infection were advanced cancer, 4; underlying cardiac disease, 7; respiratory failure, 4; pulmonary embolism, 2; multiple organ failure, 3; gastrointestinal bleeding, 1; small intestinal infarction, 1; and massive aspiration, 1. The infections that preceded death in the other 21 patients were organ space SSI, 9; pneumonia, 3 (1 with advanced cancer); bloodstream infection, 4 (2 with advanced cancer); sepsis without diagnosed infection, 4 (1 with preexisting hepatic failure and 1 with advanced cancer); and incisional SSI, 1. The rate of death following any infection was 21 (11%) of 194, and for patients without any serious infection was 23 (2.3%) of 983. The number of patients classified as having sepsis syndrome was 10 (2.5%) in the placebo group, 13 (3.3%) in the 0.5-mg/kg PGG-glucan group, and 6 (1.6%) in the 1.0-mg/kg PGG-glucan group.

PGG-glucan was well tolerated. Discontinuation of study drug owing to adverse effects occurred in 8 (2%) of 396 placebo patients, 14 (4%) of 396 patients in the 0.5-mg/kg group, and 26 (7%) of 385 patients in the 1.0-mg/kg group ($P<.003$). There was a slight increase in fever, hypertension, nausea, and vomiting seen primarily in the 1.0-mg/kg dose group. Serious adverse events were common in all groups, 253 (64%) of 396, 241 (61%) of 396, and 259 (67%) of 385, in the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively, reflecting the serious operations and high-risk nature of the patients, and were not different between groups.

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COMMENT

This study confirms the criteria used to select a high-risk patient population. Infection rates and/or death among all patients randomized and in the colorectal stratum did not achieve a statistically significant reduction in the PGG-glucan groups compared with placebo. However, the prospectively defined stratum of patients having noncolorectal procedures exhibited a relative reduction of 39% in serious infections and death in the groups treated with PGG-glucan (Table 5, $P<.02$).

The therapeutic effect of PGG-glucan was evident at both doses (0.5 mg/kg and 1.0 mg/kg). Adverse events were not significantly different between placebo and active treatment groups for most categories in this study. Because the mechanism of action for PGG-glucan involves priming of macrophages and neutrophils, one could speculate that it would increase the incidence of the systemic inflammatory response syndrome in this high-risk patient population. It is reassuring that there was no trend in this direction with observed rates of sepsis syndrome. This is consistent with the known mechanisms of action of PGG-glucan, which enhances phagocytosis and killing by monocytes but does not increase production of interleukin 1 or tumor necrosis factor.[6-8]

Why would this agent be effective in reducing infections in the noncolorectal stratum but not in the colorectal stratum? Answers are speculative, but the differences in the prevalence of important risk factors between the 2 strata may provide clues. Surgical injury causes immunosuppression[18-20] followed by enhanced immune responsiveness. This effect is greater after substantial trauma[18,21] or longer, more complex operations. In this trial, surgery duration (>3 hours) contributed significantly to infection risk, with an odds ratio of 2.46 ($P<.001$). The mean duration of surgery in the noncolorectal stratum was 3.9 hours compared with the 2.9 hours for the colorectal stratum ($P<.001$).

Fifty-four percent of noncolorectal patients were malnourished, a known risk factor for several postoperative complications, especially infection.[22,23] Malnutrition reduces immune competence[24-26] and impairs macrophage function.[26] PGG-glucan enhances leukocyte function in both normal[7] and malnourished[27,28] rats. The reduction in serious infections in patients undergoing high-risk noncolorectal gastrointestinal procedures is consistent with the mechanism of action of PGG-glucan.

Finally, SSIs that complicate colorectal surgery may result from wound contamination with high titers of bacteria, while infections after noncolorectal gastrointestinal procedures are related to the inherent complex nature of the procedures and the higher risk status of the patients undergoing these procedures. An immune modulator that enhances phagocyte activity may have limited success in containing the high levels of bacterial contamination associated with colorectal surgery,[10] but may be able to enhance the natural immune mechanisms that are compromised in the noncolorectal procedures.

Decades of experimental and clinical investigations into the prevention of postoperative infection have resulted in marked reductions in infections in all risk categories,[29] Nevertheless, a definable risk of infection remains for virtually all surgical procedures, and in selected populations, such as those defined here, the risks are considerable. While refinements in surgical techniques and antimicrobial prophylaxis will certainly occur, this study suggests that the next major advancement in the prevention of postoperative infection will occur in the context of immunomodulation. Additional investigations in the use of PGG-glucan and other immunomodulating agents are clearly warranted.

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